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10/574,645	08/10/2006	David Salomon	251206	9318

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LEYDIG, VOIT & MAYER, LTD.
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,645	SALOMON ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-15 and 17-26* is/are pending in the application.

4a) Of the above claim(s) *7-14 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15 and 17-20* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/14/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to paper filed 5/14/2008.

Claim 1 has been amended to limit the assay to SEQ ID NO 1 and detecting of neuroAIDS. The amendment has further required increased expression of SEQ ID NO 1 at levels 2.5 times greater than control.

The written description rejection has been withdrawn in view of the amendment.

Claim 16 has been canceled.

Claims 7-14 and 21-26 are withdrawn from consideration.

Claims 1, 15, 17-20 are being examined.

Claim Objections

1. Claim 15 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 15 is dependent on claim 1 and requires assaying the expression level of SEQ ID NO 1, however claim 1 requires assaying expression of SEQ ID NO 1. Thus claim 15 fails to further limit claim 1.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 15, and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method of detecting neuroAIDS disease in a mammal comprising assaying the expression level of a SEQ ID NO 1 in the central nervous system of the mammal wherein 2.5 overexpression of SEQ ID NO 1 relative to expression of SEQ ID NO 1 in "any" control sample from any tissue from any subject is indicative of neuroAIDS disease in the mammal.

It is noted that applicant elected overexpression of Cripto-1, which is SEQ ID NO 1 of the instant claims. However, the claims recite the non-elected invention of assaying copy number as well.

The claims are drawn detection in "any" mammal, although claim 17 draws the claim to humans. Thus the claims broadly encompass detecting the human Cripto-1 gene (SEQ ID NO 1) dog, cat mouse, whale, etc and comparing to "any" control sample of any tissue.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches in example 2 a study of 5 pig tailed Macaque. The study compares the expression of RNA isolated from the parietal cortex of 1 control uninfected Macaque with expression from 4 macaque infected with SHIV by use of human cytokine cDNA array (see paragraph 0073). The specification further teaches, "a more stringent 2.5 difference was chosen as an arbitrary cutoff value for differences in gene expression." (see paragraph 0073). The specification further teaches the relative expression was calculated by use of normalization spots and standard housekeeping genes.

The specification teaches in Table 2 there was a 9.56 fold increase in Tetracarcinoma-derived growth factor (Cripto-1) in the 4 SHIV infected macaque relative to the uninfected macaque.

The specification teaches, " the function of Cripto in neurons in the adult brain and its upregulation in the brains of SHIV-infected macaques are also unknown" (see paragraph 0086).

Presence and absence of working examples

The specification teaches a single study involving 4 SHIV infected macaque and 1 non-infected control in which macaque homologs of nucleic acid that haybridize to SEQ ID NO 1 reagents are upregulated. However, this study uses a single control that has not been infected with any virus. Further this study examines tissue that has been collected post-exsanguinations and thus altered expression may merely be differences in the handling of the one control sample.

The recitation of "control" sample broadly encompasses any sample from any source and is not limited by the claim to mammals that have not been infected, nor does the claim require the control sample be from the same species or tissue. Thus the recitation of control sample broadly encompasses comparing the expression of SEQ ID NO 1 to any sample from any subject including those that don't express SEQ ID No 1.

The specification does not teach any working examples of diagnosis based on detection of overexpression of SEQ ID NO 1. The specification does not teach detection of SEQ ID NO 1, but the use of a human cDNA array and primers to the cripto-1 human sequence to detect the macaque homolog of SEQ ID NO 1, which is different than SEQ ID No 1 as discussed in the state of the art section below.

The specification does not teach the detection of SEQ ID NO 1, but an analysis of an array that identified cripto-1 as a gene of interest and subsequent studies

using PCR amplification of primers specific to human cripto-1 in macaque, but has provided no documentation that the primers amplified SEQ ID No 1 and not the macaque homolog of cripto-1.

The specification does not teach any studies in humans.

The specification is silent to the house keeping gene used to normalize the expression data.

The state of prior art and the predictability or unpredictability of the art:

Sequence analysis by blast (blast.ncbi.nlm.nih.gov/Blast.cgi, 9/4/2008, pages 1-32) teaches that SEQ ID NO 1 is not the macaque cripto gene but has regions of 95% identity, but numerous gaps and regions with as little as 76% identity. Thus the BLAST analysis teaches that SEQ ID No 1 is not the macaque Cripto-1 gene and presumably was not being detected in the macaque models. Thus it would be unpredictable to associate the expression of a SEQ ID NO 1 with detection of a NeuroAIDS as the specification does not teach detection of SEQ ID NO 1, but amplification of a macaque homolog that is amplified by primers to a fragment of the human cripto-1 gene or genes that hybridize to a probe for the human Cripto-1 cDNA.

Vandesompele teaches, " Accurate normalization of gene expression levels is an absolute prerequisite for reliable results, especially when the biological significance of subtle gene expression differences is studied" (see page 9, 2nd column, discussion) (Vandesompele et al (Genome Biology (2002) volume 3 , pages 1-11). Vandesompele teaches, " That the conventional use of a single gene normalization leads to relatively large errors in a significant portion of samples tested" (see abstract, results).

Vandesompele teaches that ACTB (beta actin) appears to be the one of the worst genes fro normalization and thus resulting in large normalization errors (see page 10, 1st paragraph). Vandesompele teaches at least 3 housekeeping genes are required for accurate normalization (see page 10, 1st column, 1st full paragraph). Vandesompele thus teaches that studies of gene expression using a single gene for normalization are unpredictable due to the large variation in the expression of the genes used for normalization.

Because the claims encompass any level of increased gene expression, it is relevant to point out that the post-filing art of Cheung et al (Nature Genetics (2003), volume 33 pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of *ACTG2* in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a phenotype.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of pathology (2001) volume 195, pages 53-65). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics'

informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion).

The prior art of Newton et al (Journal of computational biology (2001) volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed one of skill in the art would first have to determine if a predictive relationship exists between overexpression of SEQ ID NO 1 and neuroAIDS. This would be unpredictable as the specification teaches a single study of 4 macaque infected with SHIV compared to a single control that was not infected. A single experiment with such a small size sample cannot be reasonably extrapolated to any mammals. First the specification used primers and /or probes to human cripto-1, which is SEQ ID No 1, however the studies were done in macaque and

would not have detected SEQ ID NO 1, but the macaque homolog, which is quite different as demonstrated by the BLAST alignment. Further the expression of the cripto-1 homolog may be a result of the viral infection, exsanguinations, or handling of the sample as gene expression in general is variable and the specification teaches macaque are out bred models, suggesting greater variability in gene expression patterns. Second the art nor the specification suggests that macaque are a reasonable model for any mammal let alone humans.

Further there is no evidence in the specification or art that the neuroAIDS induced by the SHIV infection is representative of neuroAIDS in any other species. The specification teaches a study of 5 macaque, 1 control and 4 infected.

Further the artisan would have to determine which control sample would allow for predictable determination of NeuroAIDS. This would require unpredictable trial and error experimentation as the claims nor specification provide specific guidance as to what control samples are suitable for the comparison. Thus the artisan would have to determine if a control is uninfected tissue from the central nervous system of the same species of animal, a plasmid that contains a Cripto-1 homologue of the species being assayed, a tissue sample from the animal thought to be infected that is not affected by AIDS or infection by HIV or SHV, etc. This would be undue trial and error experimentation to determine the proper control. Further the control would require normalization that is unpredictable without specific guidance as Newton, Wu and Cheung teach.

Further the skilled artisan would have to determine what level of "2.5 fold overexpression" is required to result in a predictable association of Cripto-1 and neurodegenerative disease. This would be unpredictable as the specification teaches a single study with 1 control and 4 infected macaque. Cheung teaches that there is natural gene variation among individuals, thus the teachings of Cheung suggests the non-treated macaque may simply be an outlier. Further the specification and claims do not set forth what is required for Cripto-1 to be overexpressed, although the specification does teach an "arbitrary" 2.5 fold increase in expression. Thus the skilled artisan would have to determine what level of over expression is required to be correlated with neurodegenerative disease. This would further be unpredictable as the specification not claims teach what genes were used to normalize the expression data between samples and Vandesompele teaches normalization of data is critical and improper normalization can result in large errors in data and experimental interpretation. Finally the overexpression is unpredictable as Newton and Wu suggest that gene expression data is often skewed by the data selected and must be replicated, and the instant study doe not appear to have been in any model system.

Finally instant claims and specification do not set forth any nexus for the role of increased SEQ ID NO 1 and neuroAIDS. The skilled artisan would thus have to determine if altered SEQ ID NO 1 expression is a correlated with neuroAIDS, merely a result of the infection, tissue handling or normal variability of gene expression. As the specification and art set forth no mechanistic or hypothesized link as to the role of increased SEQ ID NO 1 in neuroAIDS, the skilled artisan would have to determine if

there is a casual relationship between SEQ ID NO 1 expression levels and neuroAIDS. In view of teachings of the art as to the variability of expression data as a whole, the limited population studied, and the use of a single control, the skilled artisan would have to undertake unpredictable and undue trial and error experimentation to determine if such a relationship exists in mammals. This would be unpredictable as in the single study taught by the specification SEQ ID NO 1 was not detected, but macaque homologs that hybridize to reagents for SEQ ID NO 1.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response correctly denotes on page 6 that claim 1 has been amended to limit the claims to neuroAIDs and a 2.5 fold increase in expression of SEQ ID NO 1 relative to a control sample. While the amendment has narrowed the claims, the recitation of a control sample still raises issues of unpredictability. The claims do not require control sample is from a mammal, the central nervous system, or even a mammal that has not been infected with SHIV or any other neurotrophic virus. It would unpredictable to use "any" sample as a control without specific guidance in the claims or specification.

The response asserts that while the office has presented arguments as sample size and unpredictability of gene expression to a particular phenotype, the cited art does not provide specific evidence to question the ability of CRIPTO-1 gene expression or copy number to detect neuroAIDS. These arguments have been thoroughly reviewed but are not considered persuasive as in response to restriction applicant elected over expression of Cripto-1, thus arguments to copy number are beyond the scope of the elected invention. Further the amendment has limited the claims to neuroAIDS from the broad genus of neurodegenerative diseases. The examiner admits there is no prior art or post-filing art except applicants own study that was subsequently published based on the data of the instant specification. However, as noted above the claims are drawn to detection of SEQ ID NO 1 and the instant specification does not provide any support for detection of SEQ ID No 1, but merely teaches using primers and/or probes to detect the macaque homolog of SEQ ID NO 1 in the single example. The BLAST alignment teaches the macaque homolog of Cripto-1 is substantially different than SEQ ID No 1. Further as the instant study has not been replicated and thus has not been validated as Newton teaches is required for a predictable study. Neither the specification nor response have provided evidence that the increased expression of the macaque nucleic acid that is detected by reagents for human Cripto-1 induced by SHIV infection of the specification is indicative of detection of neuroAIDS, further as outlined above the instant specification does not provide any studies in which SEQ ID NO 1 was detected, but only the detection of macaque homologs of cripto-1.

The response continues, "The Office is reminded that the applicant does not have to prove that a correlation exists between a particular activity and an asserted use of a compound as a matter of statistical certainty." These arguments have been thoroughly reviewed but are not considered persuasive as arguments are drawn to the use of a compound and the activity of the compound, however the instant claims are drawn to methods of detecting neuroAIDS based on expression of SEQ ID NO 1. Thus the arguments to a compound and its use or activity are not applicable to the instant analysis. The instant claims are not drawn to an activity and asserted use, but expression of a nucleic acid and disease diagnosis. Further the recited references are drawn to utility rejections and thus are not germane to the instant enablement rejection.

The response concludes by asserting that SIV and SHIV are well established models of HIV infection in humans and provides several references suggesting that these are valid models of human HIV and the disclosure is translatable to humans. These arguments have been thoroughly reviewed but are not considered persuasive as Raghavan et al (Brain Pathology (1997) volume 7, pages 851-861) teaches a comparison of SHIV infection on pig tailed macaque compared to rhesus macaque. Raghavan teaches, "our data show a clear contrast in the neuropathogenesis of SHIV infection in pig-tailed and rhesus macaque (page 858, 2nd column, 1st paragraph). Raghavan teaches that the pig tailed macaque the virus failed to become active, while in the rhesus macaque there was lentiviral replication which was accompanied by brain legions (page 858, 2nd column). Thus it would be unpredictable to correlate the expression of a gene in one species of macaque with any other mammal when

Ragahavan teaches the SHIV has different affects on two members of the macaque family and is thus unpredictable in maccaques. Ragahavan teaches the SHIV infection differed from the SIV infection of the brain as SHIV infected macaques lacked meningeal inflammation that is observed in SIV. Ragahavan suggests the SIV and SHIV induced neuroAIDS have different pathologies. Thus it would be unpredictable to associate a finding based on one virus known to cause neuroAIDS, when Ragahavan teaches these are differences in responses.

Further, Enard et al (Science (2002) volume 296, pages 340-343) teaches that intraspecies variation in gene expression in brain tissue is substantial (page 340, 3rd column). Enard continues, "one human brain sample differs more from the other human samples than the latter differ from the chimpanzee samples. However, for both the brain and liver samples, the humans, as well as the chimpanzees, fall into two mutually exclusive groups when their gene expression patterns are related to that seen in the orangutan, which is evolutionarily further, removed from humans and chimpanzees than these are from each other." Thus it would be unpredictable in view of Enard to extrapolate the teachings based on a single control in one species due to the intraspecies variability in gene expression in brain, but it would be further be unpredictable to do such extrapolation to other mammals, as there is great variability between primates as demonstrated by differences between orangutan, chimpanzees, and humans. Further comparison of chimpanzees to human and macaque resulted in a 5.5 fold difference in expression. Thus it would be unpredictable to extrapolate the findings of a single finding using a single macaque as a control when the art teaches

there is substantial intraspecies variation and suggests it would further be unpredictable to make interspecies comparison based on the teachings of Enard.

Thus the rejection is maintained in view of the amendment and arguments. It would be unpredictable to use a single study in macaque for the detection of the macaque homolog detected by reagents to human cripto-1 with a single control animal to extrapolate to any other mammal, or the use of SEQ ID NO 1 as a marker, when the study did not detection SEQ ID No 1, but a homolog. Further the teachings of Enard and Raghavan demonstrate unpredictability of different SHIV infection in different species of macaque and intraspecies and interspecies variability gene expression.

Summary

No claims are allowed.

Conclusions

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Sarae Bausch/
Primary Examiner, Art Unit 1634